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10/523,292	02/03/2005	Guillermo Oliver	SJ-02-0011A	1276

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	**PAPER NUMBER**
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,292	OLIVER ET AL.	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *6-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group II (claims 1-5, to the extent the clams are drawn to methods of detecting Prox1 protein) in the reply filed on 5/7/2007 is acknowledged. The traversal is on the ground(s) that applicants understand the common technical feature of the groups to be the expression of Prox1 in the lymphatic tissue of a tumor, and not that of using Prox1 expression as a marker for lymphatic precursor cells, which the examiner notes is known in the art. This is not found persuasive because applicants have not provided objective evidence for why it would not be expected by one of ordinary skill in the art to find Prox1 expression in lymphatic tissue associated with a tumor, when the prior art has shown that Prox1 expression is associated with lymphatic development.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-11 are pending.

Claims 6-11 and claims 1-5(to the extent the claims read on measuring Prox1 mRNA), are withdrawn from consideration.

Claims 1-5(to the extent the claims read on measuring Prox1 protein) are examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is not clear how detecting the expression of Prox1 protein in a sample from a tumor results in the determination of the extent of lymphatic involvement in a tumor. The lack of clarity results from the lack of a recitation of how to correlate the active step with the stated purpose of the method, and because it is not clear what is actually meant by the phrase "the extent of lymphatic involvement in a tumor". Does this phrase include an assessment of lymph node involvement, and therefore a prognosis for the cancer?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the detection of Prox1 protein for the purpose of detecting the presence of lymph vessel endothelial cells within a tumor, does not reasonably provide enablement for using the measurement of Prox1 protein for the purpose of assessing the extent of lymphatic involvement in a tumor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is that the specification fails to enable claims to methods that have the purpose of assessing lymphatic involvement, because the phrase "lymphatic involvement" includes an assessment of lymph node status of a

patient having a tumor, and the phrase "extent of lymphatic involvement" includes a quantitative correlation between Prox1 protein expression and lymphatic involvement.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The claims appear to read on methods that the intended use of using a measurement of an amount of Prox1 protein as a method for assessing the prognosis of a cancer patient. The claims have the intended use of "determining the extent of lymphatic involvement", which includes within its scope an assessment of lymph node status of a tumor. Furthermore, dependent claims 2 and 3 are drawn to methods comprising the active steps of measuring the amount of Prox1 protein and quantitatively detecting Prox1 expression.

The specification lacks any evidence that there is a quantitative association between Prox1 protein levels and any measure of tumor prognosis or lymph node status. Furthermore, the specification lacks a definition of the scope of the phrase "determining the extent of lymphatic involvement" in a tumor and how detecting expression of Prox1, or quantitatively measuring Prox1 protein levels may be used to determine the extent of lymphatic involvement. The specification does present data showing the Prox1 can be used to identify lymphatic endothelial cells and shows that lymphatic endothelial cells may be detected in tumor samples, but this is qualitative data from which one of skill in the art may conclude that Prox1 detection may be used

to detect the presence of lymphatic endothelial cells within a tumor. The use of a quantitative measurement of Prox1 protein levels has not been established as a marker for lymph node involvement or for cancer prognosis. The prior art (see below) has established that Prox1 is detected in lymph vessels associated with various tumors. However, the prior art has not provided the specific teaching that measurement of Prox1 protein levels may be used as a basis for a cancer prognosis or as an assay of lymph node status. Reis (Reis, R.M. et al. Pathology Research and Practice, 201: 771-776, 2005) teaches that Prox-1 is also expressed in some non-endothelial cells such as hepatocytes, bile ductum epithelium, pancreatic epithelium, central nervous system, lens, retina, and cardiomyocytes in avian and murine embryos, and suggests caution in using Prox1 as a lymphatic marker in vascular neoplasms, but that it may be reliably used in non-vascular tumor and reactive/inflammatory samples (see page 775, 1st and 2nd column).

In view of the nature of the claimed inventions, that the claims are drawn to methods that appear to require a detection of a quantitative association between Prox1 protein levels and an "extent of lymphatic involvement" in a tumor, which is an undefined endpoint, and in view of the caution suggested by Reis, it would require further experimentation by one of skill in the art to practice the full scope of the invention as claimed. This further experimentation appears to be undue experimentation because it is experimentation of the invention itself to establish a quantitative relationship between a prognosis for any and all cancers and Prox1 protein levels.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Papoutsi (Papoutsi, M. et al. Histochem. Cell Biol. (114: 373-385, 2000).

Claim 1 is drawn to a method comprising an active step of detecting Prox1 expression in a tumor. Claim 4 is drawn to a method wherein the expression of Prox1 is detected with a marker that binds to Prox1 and can be visualized.

Papoutsi detects Prox1 in a tumor formed by A375 melanoma cells grown on an avian chorioallantoic membrane (CAM) using a polyclonal antibody that binds Prox1 and is visualized by a fluorescent secondary Cy3-conjugated goat anti-rabbit antibody (see page 375, 2nd column, and page 379, Figure 4). Therefore, Papoutsi teaches a method that is the same as that claimed.

6. Claims 1 and 4 are rejected under 35 U.S.C. 102(a) as being anticipated by Carreira (Carreira, C.M. et al., Cancer Res. 61: 8079-8084, 2001, Nov. 15) or Padera (Padera, T.P. et al. Science, 296: 1883-1886, 2002, June 7; cited in IDS).

Claim 1 is drawn to a method comprising an active step of detecting Prox1 expression in a tumor. Claim 4 is drawn to a method wherein the expression of Prox1 is detected with a marker that binds to Prox1 and can be visualized.

Carreira detects Prox1 in samples from hepatocellular carcinoma (HCC) using a polyclonal antibody that binds Prox1 and is visualized by a peroxidase/diaminobenzidene system (see page 8080, 1st column, and page 8081-8082 and Figure 3). Therefore, Carreira teaches a method that is the same as that claimed.

Padera detects Prox1 in samples of tumor xenografts (see page 1883, 2nd column and Figure 1. Padera detects Prox1 in samples of lung tumors in patients (see page 1884, 2nd-3rd column. The antibody to Prox1 could be visualized as a brown nuclear stain. Therefore, Padera teaches a method that is the same as that claimed.

7. Claims 1 and 4 are rejected under 35 U.S.C. 102(a) as being anticipated by Wilting (Wilting, J. et al. The FASEB Journal express article 10/1096/fj.01-1010fje. Published online June 7, 2002; cited in IDS).

Wilting teaches the detection of Prox1 in specimens of lymphangiomas and hemangiomas using a Prox1 polyclonal antibody that was detected by binding of secondary Cy2- and Cy3- conjugated goat-anti-rabbit or goat-anti-mouse antibodies (see page 3 of document and page 4 of document). Therefore, Wilting teaches a method that is the same as that claimed.

8. Claims 1 and 4 are rejected under 35 U.S.C. 102(a) as being anticipated by Wigle (Wigle, J.T. et al., The EMBO Journal, 21: 1505-1513, 2002, April; cited in the IDS).

Wigle teaches the detection of Prox1 in tumor samples from A431 tumor xenografts and from lymphomas developed in the leg of an Ink4d mutant mouse (see pages 1508-1509) using a

rabbit anti-Prox1 antibody that was detected using an anti-rabbit goat Cy3-conjugated antibody. Therefore, Wigle teaches a method that is the same as that claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papoutsi (supra), Carreira (supra), Padera (supra), Wilting (supra) or Wigle (supra) in view of Roitt (Roitt, I. Et al. Immunology, Third Edition, Mosby, St. Louis, 1993, see pages 25.4-25.5).

Claims 1, 4 and 5 encompass methods where the detection of Prox1 expression is with an anti-Prox1 antibody that is fused to a marker that can be visualized.

Each of Papoutsi (supra), Carreira (supra), Padera (supra), Wilting (supra) and Wigle (supra) teach methods of detecting Prox1 using indirect detection methods, where an unlabeled anti-Prox1 antibody is reacted with the samples and then detected using a labeled secondary antibody. Therefore, each of Papoutsi (supra), Carreira (supra), Padera (supra) and Wilting (supra) fails to teach a method of detecting Prox1 using an antibody that is fused to a marker than can be visualized. However, the use of direct detection methods for detection of antigens is known in the art, and appears to be an alternative to the use of indirect methods. For example, Roitt teaches that an antibody may be directly labeled or may be detected by binding of a labeled secondary antibody (see Figure 25.8). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of any of Papoutsi (supra), Carreira (supra), Padera (supra), Wilting (supra) and Wigle (supra) with that of Roitt to make a method that used a labeled primary antibody. One would have been motivated by the fact that in a direct labeling technique there are less steps required for visualization because there is no need to use a secondary antibody.

10. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Papoutsi (supra), Carreira (supra), Padera (supra), Wilting (supra) or Wigle (supra) in view of Milde-Langosch (Milde-Langosch, K. et al., Breast Cancer Research and Treatment, 67: 61-70, 2001) or Takenoue (Takenoue, T. et al., Annals of Oncology, 1: 273-279, 2000).

Claims 1-4 encompass methods where the detection of Prox1 expression is quantitative, because claim 2 recites that an amount of Prox1 protein is measured and because claim 3 recites that expression of Prox1 is detected quantitatively.

Each of Papoutsi (supra), Carreira (supra), Padera (supra), Wilting (supra) and Wigle (supra) teach methods of detecting Prox1 via immunohistochemistry, but fails to explicitly teach a methods of detecting Prox1 protein amounts or detecting Prox1 quantitatively. However, methods for quantitative immunohistochemistry also the use of Western blot analysis of extracted proteins are known in the art as evidenced by the teachings of Milde-Langosch (see page 62 and 63, also Table 1 and Table 2) or Takenoue (see page 274, abstract, and page 278, Figures 5 and 6). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of any of Papoutsi (supra), Carreira (supra), Padera (supra), Wilting (supra) and Wigle (supra) with that of Milde-Langosch or of Takenoue to make a method that resulted in the quantitation of Prox1 protein levels and the detectioin of Prox1 expression quantitatively. One would have been motivated to make the method of detection of Prox1 quantitative by the desire to find whether a correlation exists between Prox1 protein expression and a parameter of tumor prognosis.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
June 12, 2007

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER